

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214018Orig1s000

OTHER REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology (OSE)
Office of Pharmacovigilance and Epidemiology (OPE)

Epidemiology: Review of proposed real-world evidence study

Date: February 5, 2021

Reviewer: Catherine Lerro, PhD, MPH
Division of Epidemiology I (DEPI-I)
Office of Surveillance and Epidemiology (OSE)

Team Leader: Catherine Callahan, PhD, MA
DEPI-I, OSE

Associate Directors: Wei Hua, PhD
DEPI-I, OSE

Jie (Jenni) Li, PhD
Real World Evidence,
Office of Pharmacovigilance and Epidemiology

Subject: Review of RWE related to fosdenopterin NDA application for
treatment of molybdenum cofactor deficiency Type A (MoCD
Type A)

Drug Name: Fosdenopterin (Nulibry)

Orphan Designation: #09-2912

Application Type/Number: NDA 214018 / IND 117502

Applicant/sponsor: Origin Biosciences, Inc.

OSE RCM #: 2020-396

SUMMARY

On January 6, 2020, the Division of Rare Disease and Medical Genetics (DRDMG) notified the Division of Epidemiology I (DEPI) that the FDA Real World Evidence (RWE) Subcommittee would review the Sponsor's proposed use of RWE to assess the safety and efficacy of fosdenopterin (NULIBRY, Origin Biosciences, Inc.) to support the NDA for the treatment of molybdenum cofactor deficiency Type A (MoCD Type A).

MoCD Type A is an ultra-rare, rapidly progressive, chronic, and mostly fatal disease associated with autosomal recessive inborn error of metabolism that typically exhibits an acute onset in neonates or in early infancy. Incidence estimates for MoCD Type A range from 1 in 341,690 to 411,187. Using the current estimate of the incidence of MoCD Type A and year-over-year survival probabilities from a natural history study, it is estimated that as of the beginning of 2020 there are currently between 45 and 54 individuals with MoCD Type A under 10 years of age in the US.¹ Characteristics of the disease include gross destruction of the brain due to elevated levels of sulfites, intractable seizures, metabolic acidosis, exaggerated startle reactions, axial hypotonia with limb hypertonia, failure to thrive, poor or halted feeding response, and high-pitch crying. There are no approved medical products for patients with MoCD Type A, with current treatment option intended to provide relief from symptoms or clinical manifestations of the disease. In the absence of treatment, patients usually die in the first year of life.²

MoCD Type A is an exceedingly rare, rapidly progressive, and fatal disease with no approved treatment; fosdenopterin has been approved for orphan designation. The clinical program for fosdenopterin demonstrates a survival benefit of the drug. As such, it would be both unethical and logistically challenging to conduct a placebo-controlled clinical trial for fosdenopterin. Instead, the Sponsor's NDA submission includes results from single-arm trials with external real-world data comparators. There is also supportive evidence from a mechanistic study related to the pathophysiologic pathway for the disease.

The attached slides (Appendix 1) present DEPI's synopsis of the proposed study, along with a high-level appraisal of the strengths and limitations of the proposal. These slides were presented at the internal briefing to discuss this proposal with OSE leadership on January 13, 2020, and at the RWE Subcommittee meeting on January 15, 2020.

The pooled single-arm trials demonstrated substantial survival benefit with fosdenopterin treatment compared to the external control arm. **DEPI concluded that the limitations of using an external control arm do not outweigh the strong survival benefit that was observed among patients treated with fosdenopterin, considering the rarity and severity of MoCD Type A. DEPI also concluded that the draft NDA integrated review for fosdenopterin appropriately described these limitations and incorporated them into the risk-benefit assessment.**³

¹ Origin Biosciences, Inc., 2.5 Clinical Overview, NULIBRY (fosdenopterin), filed under NDA 214018 on May 5, 2020.

² Ibid

³ Nulibry (fosdenopterin) Integrated Review, NDA 214018, anticipated review completion date February 26, 2021 (unfiled).

Appears this way on original

Nulibry (fosdenopterin) for treatment of MoCD Type A

DEPI review of RWE submitted for NDA filing

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MoCD Type A

- Molybdenum cofactor deficiency (MoCD) Type A
 - Autosomal recessive inborn error of metabolism
 - Ultra-rare, rapidly progressive, chronic, and mostly fatal
 - Acute onset in neonates or early infancy
 - Incidence: 1 in 341,690 to 411,187
 - Prevalence: 45 to 54 individuals in the US under age 10
 - Patients experience intractable seizures, metabolic acidosis, failure to thrive, feeding difficulties, axial hypotonia and ***early death from the accumulation of toxic metabolites, primarily S-sulfocysteine (SSC), in the central nervous system***
 - No approved treatments

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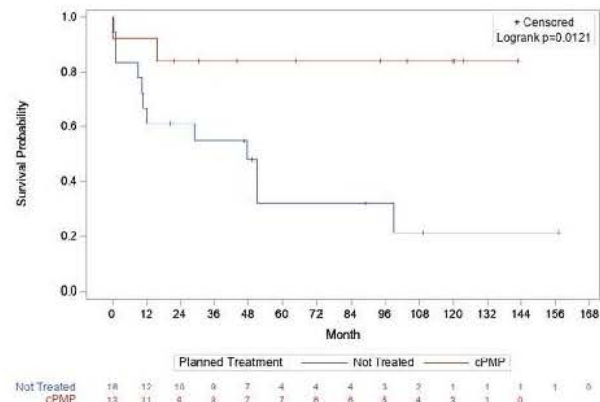
Nulibry (fosdenopterin)

- Chemically synthetic form of cyclic pyranopterin monophosphate (cPMP)
- Treats MoCD Type A by replacing the cPMP substrate, permitting the remaining MoCo synthesis steps to proceed
- Leads to
 - Activation of the MoCo-dependent enzymes (e.g. sulfite oxidase)
 - Elimination of sulfites and secondary metabolite SSC
- Orphan drug (2009), breakthrough (2013), and rare pediatric disease designations (2017)
- PDUFA Action Date: February 26, 2021

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Nulibry Efficacy Study

- Study population: Nulibry patients from 3 single-arm trials and untreated natural history controls
 - Nulibry treated: 13
 - Total natural history control set: 37
 - Genotype-matched controls: 18
- Primary endpoint: overall survival
- Mean survival time at 36 months
 - Nulibry: 32 months
 - Natural history controls: 24 months
- Hazard Ratio= 0.18 (95% CI: 0.04-0.72)



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RWE Strengths

- Results demonstrate statistically significant finding for Nulibry efficacy
- Logistical and ethical challenges of an RCT
 - Survival benefit, with no other treatment currently available
 - Extremely rare and rapidly progressive disease
- Study strengths
 - Genotype-matched and weighted analyses to control for potential confounding related to disease severity
 - Sensitivity analyses
- Confirmatory biomarker evidence
 - Reduction of urinary SSC concentrations (normalized to creatinine) in all Nulibry patients
 - Sustained with long-term treatment (up to 7 years)

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RWE Limitations

Non-comparability

- Untreated more likely to be male, earlier birth cohort, non-white race
- Genotype matching to minimize bias
 - Genotype predicts disease phenotype
 - 9/13 patients have at least one exact phenotype match
 - Rest matched to untreated patients w/ mutations thought to have similar impact on protein function

Characteristic	Fosdenopterin (N=13)	Untreated FAS (N=37)	Untreated GMAS (N=18)
Sex			
Male	7 (53.8%)	28 (75.7%)	13 (72.2%)
Female	6 (46.2%)	9 (24.3%)	5 (27.8%)
Birth Year			
≤1999	0	7 (18.9%)	2 (11.1%)
2000-2004	0	1 (2.7%)	0
2005-2009	3 (23.1%)	17 (45.9%)	9 (50%)
2010-2014	8 (61.5%)	12 (32.4%)	7 (38.9%)
≥2015	2 (15.4%)	0	0
Race			
White	10 (76.9%)	21 (56.8%)	11 (61.1%)
Asian	3 (23.1%)	10 (27%)	4 (22.2%)
Other	0	6 (16.2%)	3 (16.7%)
Ethnicity			
Hispanic	1 (7.7%)	2 (5.4%)	0
Non-Hispanic	12 (92.3%)	31 (83.8%)	14 (77.8%)
Unknown	0	4 (10.8%)	4 (22.2%)
Region			
North America	2 (15.4%)	3 (8.1%)	0
Europe	6 (46.2%)	14 (37.8%)	8 (44.4%)
Rest of World	5 (38.5%)	20 (54.1%)	10 (55.6%)

RWE Limitations

Confounding

- Genotype, age at onset, healthcare access
- Difficult to control for potential confounders using traditional methods due to small sample size
 - Adjustment, stratification, matching (used for genotype), propensity-score methods
- Residual confounding from imperfect genotype match
 - May not fully capture treated/control differences in disease phenotype

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RWE Limitations

Survival bias

- Is there a spurious mortality benefit from diagnosing and treating patients who would have less severe disease course if left untreated?
- Unlikely a major issue in this RWE study
 - Prenatal testing did not impact disease survival
 - No indication of selectively treating patients with less severe disease
 - Early diagnosis cannot impact disease course because there is no approved treatment
 - Sensitivity analysis excluding matched pair with different date of onset- similar findings

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RWE Limitations

Post-hoc analysis plan

- SAP formulated after mortality outcomes were known
- Analyses should be specified *a priori* to minimize type I error
- FDA reviewed and agreed to SAP prior to the NDA submission

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Conclusions

- Limitations do not seem to outweigh the survival benefit of Nulibry treatment in this population
- Limitations of the RWE study have been clearly described in the clinical review and included in the risk-benefit assessment

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Backup slides

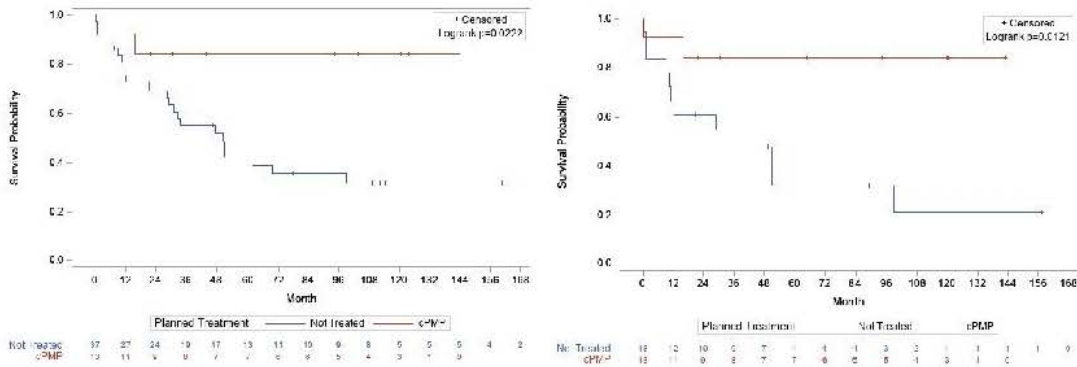
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Nulibry Relevant Regulatory History & Interactions

Date	Event
10/23/2013	BTB granted for the MoCD Type A development program
11/15/2017	Meeting to discuss the status of the clinical development program and obtain feedback from the Agency on the adequacy of clinical data obtained to support an NDA submission (Minutes 11/29/2017)
8/14/2019	Meeting to discuss the details of the proposed contents of the safety and efficacy data to be submitted in the NDA and to obtain agreement of the safety and efficacy analyses (Minutes 9/13/2019)
12/18/2019	Teleconference to discuss clinical and regulatory pre-NDA topics, including obtaining agreement on the content and format of the NDA (Minutes 12/19/2019, Briefing Package 11/18/2019)
2/26/2021	Action PDUFA Date

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Full Analysis Set vs. Genotype-Matched Set



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Characteristic	Fosdenopterin (N=13)	Untreated FAS (N=37)	Untreated GMAS (N=18)
Country of participation, n (%)			
United States	2 (15.4%)	2 (5.4%)	0
Australia	1 (7.7%)	0	0
Canada	0	1 (2.7%)	0
Germany	2 (15.4%)	3 (8.1%)	1 (5.6%)
Spain	0	1 (2.7%)	0
United Kingdom	3 (23.1%)	5 (13.5%)	2 (11.1%)
Israel	1 (7.7%)	7 (18.9%)	4 (22.2%)
Japan	0	2 (5.4%)	0
Malaysia	0	2 (5.4%)	2 (11.1%)
Netherlands	2 (15.4%)	2 (5.4%)	2 (11.1%)
Saudi Arabia	0	4 (10.8%)	2 (11.1%)
Tunisia	1 (7.7%)	3 (8.1%)	2 (11.1%)
Turkey	1 (7.7%)	5 (13.5%)	3 (16.7%)

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	MCD-501	MCD-502		MCD-503	MCD-201	MCD-202
		Retrospective	Prospective			
Study Setting	Academia	Academia	Academia	Academia	Academia	Academia
Locations	Australia, Germany, The Netherlands, Turkey, United Kingdom, United States	Canada, Germany, Spain, Israel, Malaysia, The Netherlands, Poland, Saudi Arabia, Tunisia, Turkey, United Kingdom, United States	Germany, Spain, Italy, Japan, Malaysia, The Netherlands, Saudi Arabia, Tunisia, Turkey, United Kingdom, United States	Israel, Malaysia, Saudi Arabia, The Netherlands, Turkey	Australia, The Netherlands, Tunisia, United Kingdom, United States	Israel, Turkey, United Kingdom, United States
Dates of Recruitment	09 Jul 2011 – 07 Oct 2014 ^a	24 Sep 2013 – 17 Feb 2014 ^a	24 Sep 2013 – 17 Feb 2014 ^a	21 Nov 2019 – 31 Jan 2020	02 Apr 2014 – 24 Feb 2020 ^a	04 Jul 2016 – present ^a
Dates of Exposure	06 Jun 2008 – 10 Apr 2014 ^b	Natural history study, no IP administered	Natural history study, no IP administered	Retrospective data collection; no IP administered	10 Apr 2014 – present	20 Jun 2016 – present
Dates of Follow-up	N/A ^c	N/A ^c	20 Mar 2014 – 11 Dec 2015	N/A ^c	Ongoing study	Ongoing study
Dates of Data Collection	09 Jul 2011 – 07 Oct 2014 ^d	24 Sep 2013 – 17 Feb 2014 ^d	24 Sep 2013 – 11 Dec 2015 ^d	21 Nov 2019 – 31 Jan 2020	02 Apr 2014 – present	20 Jun 2016 – present

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Table 8 Efficacy Assessments Conducted by Study

Study:	MCD-502 Natural History		MCD-501	MCD-201	MCD-202
Treatment:	None		rcPMP	Fosdenopterin	Fosdenopterin
Data Collection:	Retrospective ^a	Prospective	Retrospective ^a	Prospective	Prospective
Endpoints:					
Overall Survival	Assessed	Assessed	Assessed	Assessed	Assessed
Biomarkers					
Urine Biomarkers	As available	Assessed	As available	Assessed	Assessed
Blood Biomarkers	As available	Assessed	As available	Assessed	Assessed
Growth Parameters	As available	Assessed	As available	Assessed	Assessed
Feeding Status	As available	Assessed	As available	Assessed	Assessed
Developmental Assessments:					
GMFCS-ER	As available	Assessed	As available	Assessed	Assessed
Bayley	As available	Assessed	As available	Assessed	Assessed
WPPSI	As available	Assessed	Not assessed	Assessed	Not applicable
Denver	As available	Assessed	As available	Not assessed	Not assessed
GMFM-88	Not assessed	Not assessed	Not assessed	Not assessed	Assessed
Ability to Sit Unassisted	As available	Assessed	As available	Assessed	Assessed
PEDI	Not assessed	Not assessed	Not assessed	Not assessed	Assessed
Seizure Activity/AED use	As available	Assessed	As available	Assessed	Assessed

**D & DRUG
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Clinical Inspection Summary

Date	January 28, 2021
From	John Lee, M.D., Medical Officer Phillip Kronstein, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE)
To	Mimi Phan, Regulatory Project Manager Kathleen Donohue, M.D., Medical Officer Division of Rare Diseases and Medical Genetics (DRDMG)
Application	NDA 214018
Applicant	Origin Biosciences, Inc.
Drug	Fosdenopterin (proposed, Nulibry®)
NME / Original NDA	Yes
Review Timeframe	Priority
Proposed Indication	Treatment of Molybdenum Cofactor Deficiency Type A
Consultation Date	August 3, 2020
CIS Goal Date	January 26, 2021 (original); January 29, 2021 (extended)
Action Goal Date	February 26, 2021
PDUFA Due Date	February 28, 2021

I. OVERALL ASSESSMENT OF FINDINGS

Two studies were audited (remotely) in support of this NDA review. In auditing the two studies, two clinical investigator (**CI**) sites that participated in the interventional study (ALXN-MCD-201) and the contract research organization (**CRO**) that coordinated the natural history study (ALX-MCD-502) were selected for Good Clinical Practice (**GCP**) inspection. Remote regulatory assessments (**RRAs**) were performed in lieu of on-site inspections since on-site inspections were not achievable due to the ongoing COVID-19 pandemic-related travel restrictions.

Overall, no objectionable GCP violations were identified during the RRAs of all three entities. Based on the results of the RRAs, the clinical data generated by the two CIs and the CRO appear to be supportive of this NDA.

II. BACKGROUND

Origin Biosciences, Inc. (**Origin**) seeks to market fosdenopterin, cyclic pyranopterin monophosphate (**cPMP**) hydrobromide dihydrate (proposed trade name Nulibry®), as a treatment for molybdenum cofactor deficiency (**MoCD**) Type A (**MoCD-A**). The regulatory designations granted to Origin in developing this product include: orphan drug (2009), breakthrough therapy (2013), rare pediatric disease (2017), and priority NDA review.

MoCD-A is a rare autosomal recessive inborn error of metabolism that leads to a rapid deterioration of the central nervous system (**CNS**) and death within the first years of life. The classification of MoCD is based on the affected gene, as either Type A, B or C. The three subtypes are indistinguishable clinically and biochemically (determination by genetic testing). Current treatment options are limited to symptom-driven supportive care.

Origin proposes fosdenopterin as a novel agent that may help restore the defective metabolic pathway in the brain. Fosdenopterin therapy immediately after birth has been shown to improve the clinical outcome in limited studies collectively, of which the following six support this NDA:

- ALXN-MCD-101: *A Phase 1, Randomized, Blinded, Placebo-Controlled, Single-Dose, Sequential-Cohort, Dose Escalation Study to Evaluate the Safety, Tolerability and Pharmacokinetics of ALXN1101 in Healthy Subjects*
- ALXN-MCD-201: *A Phase 2, Multicenter, Multinational, Open Label, Dose-Escalation Study to Evaluate the Safety and Efficacy of ORGN001 (formerly ALXN1101) in Pediatric Patients with Molybdenum Cofactor Deficiency (MoCD) Type A Currently Treated with Recombinant Escherichia coli-Derived Cyclic Pyranopterin Monophosphate*
- ALXN-MCD-202: *A Phase 2/3, Multicenter, Multinational, Open-Label Study to Evaluate the Efficacy and Safety of ORGN001 (formerly ALXN1101) in Neonates with Molybdenum Cofactor Deficiency (MoCD) Type A*
- ALX-MCD-501: *A Retrospective, Observational, Noninterventional Data Collection Study for Patients with Molybdenum Cofactor Deficiency who have been Previously Treated with Cyclic Pyranopterin Monophosphate (cPMP)*
- ALX-MCD-502: *A Natural History Study of Molybdenum Cofactor and Isolated Sulfite Oxidase Deficiencies*
- ORGN-MCD-503: *Retrospective Collection of Survival Data and Historic Imaging Data from Two Studies of Molybdenum Cofactor Deficiency*

Studies ALXN-MCD-201 (fosdenopterin intervention) and ALX-MCD-502 (natural history) were audited by RRAs using electronic videoconferencing and other means of remote electronic communication. The interventional study was audited through RRAs of two CI sites: (1) Site 109, Peter Robinson (Samir Munir as CI at time of inspection), United Kingdom (**UK**); and (2) Site 330, Rim Ben Abdelaziz, Tunisia. The natural history study was audited through RRA evaluation for [REDACTED] (b) (4) the CRO that coordinated the study. Which sites and how they were to be evaluated for GCP compliance were determined based on subject enrollment and inspection feasibility during the global COVID pandemic. The two audited studies are described below.

Study ALXN-MCD-201: *A Phase 2, Multicenter, Multinational, Open Label, Dose-Escalation Study to Evaluate the Safety and Efficacy of ORGN001 (formerly ALXN1101) in Pediatric Patients with Molybdenum Cofactor Deficiency (MoCD) Type A Currently Treated with Recombinant Escherichia coli-Derived Cyclic Pyranopterin Monophosphate*

This prospective open-label study is currently on-going at five centers worldwide (UK, Tunisia, Netherlands, Australia, and United States). Seven children with MoCD-A on **recombinant** cPMP (**rcPMP**) therapy are currently enrolled, of whom five were previously enrolled in the natural history study (ALXN-MCD-501). The major objectives are: (1) to evaluate the efficacy and safety of fosdenopterin when used in lieu of rcPMP (switch therapeutic agent, from rcPMP to fosdenopterin); and (2) to compare the clinical outcome with rcPMP and fosdenopterin therapies relative to no intervention (findings of natural history study as control data). The dose of fosdenopterin was initially matched to the final dose of rcPMP and sustained for two months, then increased monthly by ≤ 240 ug/kg/day for three months based on (absence of) signs and symptoms of drug toxicity.

Based on the interim study results to date, the sponsor concludes that: (1) switching from rcPMP to fosdenopterin has no impact on treatment efficacy or safety, and (2) continued therapy with fosdenopterin leads to improvements in growth and development (new skills) even in children with previously static encephalopathy, without new safety concerns.

Study ALX-MCD-502: *A Natural History Study of Molybdenum Cofactor and Isolated Sulfite Oxidase Deficiencies*

As a natural history study, fosdenopterin (or any other therapy) was **not** used in the study. The primary study objective was to characterize the natural history of MoCD-A, the most common subtype of MoCD. A total of 65 patients were included in the study, including 37 with MoCD-A (14 prospective subjects). The findings of this natural history study provided new insight into this rare genetic disease, including new information on family history, genetic mutations, medical and/or surgical history, clinical presentation and progression of MoCD, and scope of laboratory abnormalities. The findings were consistent with the limited information available in the literature and provided more information about the clinical course of MoCD-A, including a median survival of 4.0 years.

III. INSPECTION RESULTS

1. Peter Robinson (Samir Munir)

Study ALXN-MCD-201, Site 109
South Glasgow University Hospital
Glasgow, Strathclyde G51 4TF, UK
Inspection dates: December 3-15, 2020

This RRA of the conduct of Study ALXN-MCD-201 by Peter Robinson (Samir Munir) was performed through video conferencing and electronic document sharing. The original CI (Dr. Peter Robinson) had retired, and the study responsibility had been transferred to Dr. Samir Munir in June 2020. (b) (6) subjects were enrolled and continue in the study. The scope of the RRA included informed consent, subject selection, study therapy, endpoint assessment, subject case records review, protocol compliance, and recordkeeping.

No significant GCP deficiencies were observed. Noteworthy observations consisted of minor errors or omissions in recordkeeping, typically incomplete documentation of: subject selection data, fosdenopterin dose adjustments, non-primary efficacy assessments, and non-serious adverse events. The observed deficiencies appeared unlikely to be significant. The primary efficacy endpoint data were adequately verifiable against the data reported in the NDA.

2. Rim Ben Abdelaziz

Study ALXN-MCD-201, Site 330

Tunis 1007, Tunisia

Inspection dates: January 19-22, 2021

This audit of Study ALXN-MCD-201 for Site 330 in Tunisia was conducted by RRA. (b) (6)

(b) (6) The scope of the RRA included informed consent, subject selection, study therapy, endpoint assessment, subject case records review, protocol compliance, and recordkeeping.

No significant GCP deficiencies were observed. Study records ((b) (6)) were complete, organized, and readily available for audit review. The primary efficacy endpoint data were adequately verifiable against the data reported in the NDA.

3. (b) (4)

(b) (4)

Inspection dates: (b) (4)

This audit of Study ALX-MCD-502 was conducted by RRA to confirm unbiased and adequate evaluation of the natural clinical course of untreated MoCD-A. 164 subjects were identified by literature search, 68 were screened for subject eligibility, 65 were enrolled (including 37 with MoCD-A, 14 prospective), and 62 completed the study. The audit included a comprehensive review of CI site monitoring files for: drug accountability, staff training, delegation of authority, and financial disclosures.

No significant GCP deficiencies were observed. The CRO appeared to have adhered adequately to all required and expected GCP standards in coordinating the conduct of the study: contractual agreement with sponsor, CI site monitoring, and compliance with established center standard operating procedures. Study dates, subjects, enrollment, and clinical management records were consistent with those reported in the NDA. Copies of CI site source records were not available for verification of the data provided in the NDA.

{See appended electronic signature page}

John Lee, M.D.

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Division of Clinical Compliance Evaluation
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OSI / DCCE / GCPAB / Program Analyst / Yolanda Patague
OSI / Database Project Manager / Dana Walters

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**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: January 26, 2021

To: Nicolas Kong, M.D., Regulatory Health Project Manager
Division of Rare Diseases and Medical Genetics (DRDMG)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: OPDP Labeling Comments for NULIBRY (fosdenopterin)

NDA: 214018

In response to DRDMG consult request dated July 7, 2020, OPDP has reviewed the proposed product labeling (PI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Nulibry (fosdenopterin) for injection, for intravenous use.

Labeling: OPDP's comments on the proposed labeling are based on the draft labeling received by electronic mail from DRDMG (Nicolas Kong) on January 19, 2021, and we have no additional comments at this time.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed, and comments on the proposed IFU were sent under separate cover on January 19, 2021.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on December 11, 2020, and we do not have any comments.

Thank you for your consult. If you have any questions, please contact Adewale Adeleye at (240) 402-5039 or adewale.adeleye@fda.hhs.gov.

18 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: January 19, 2021

To: Nicholas Kong
Regulatory Project Manager
Division of Rare Diseases and Medical Genetics (DRDMG)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Barbara Fuller, RN, MSN, CWOCN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon R. Mills, BSN, RN, CCRP
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Adewale Adeleye, PharmD
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Instructions for Use (IFU)

Drug Name (established name): NULIBRY (fosdenopterin)

Dosage Form and Route: for injection, for intravenous use

Application Type/Number: NDA 214018

Applicant: Origin Biosciences Inc.

1 INTRODUCTION

On June 29, 2020, Origin Biosciences Inc. submitted for the Agency's review an original New Drug Application (NDA) 214018 for NULIBRY (fosdenopterin) for injection with the proposed indication for the treatment of Molybdenum Cofactor Deficiency (MoCD) Type A, a rare pediatric disease.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Rare Diseases and Medical Genetics (DRDMG) on July 7, 2020, for DMPP and OPDP to review the Applicant's proposed Instructions for Use (IFU) for NULIBRY (fosdenopterin) for injection.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review was completed on November 25, 2020.

2 MATERIAL REVIEWED

- Draft NULIBRY (fosdenopterin) for injection IFU received on June 29, 2020 revised on October 23, 2020, and accessed from the Review Division Share Point site by DMPP on November 4, 2020.
- Draft NULIBRY (fosdenopterin) for injection, for intravenous use IFU received on June 29, 2020, revised by the Review Division throughout the review cycle, and received from DMPP by OPDP on January 14, 2021.
- Draft NULIBRY (fosdenopterin) for injection Prescribing Information (PI) received on June 29, 2020, revised by the Review Division throughout the review cycle, and accessed from the Electronic Document Room (EDR) by DMPP and OPDP on January 6, 2021 and January 19, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the IFU document using the Arial font, size 11.

In our collaborative review of the IFU we:

- simplified wording and clarified concepts where possible

- ensured that the IFU is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the IFU is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the IFU meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The IFU is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the IFU.

Please let us know if you have any questions.

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**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology**

Enhanced Pharmacovigilance Plan Review

Date: January 7, 2021

Safety Evaluator: Debra Ryan, PharmD, MBA
Division of Pharmacovigilance I (DPV-I)

Medical Officers: Ivone Kim, MD, FAAP
Melissa Reyes, MD, MPH
DPV-I

Team Leader: Carmen Cheng, PharmD
DPV-I

Associate Director: Eileen Wu, PharmD
DPV-I

Product Name: Nulibry (fosdenopterin)

Subject: Photosensitivity Reactions

Application Type/Number: NDA 214018

Applicant/Sponsor: Origin Biosciences, Inc.

OSE RCM #: 2020-2347

1 INTRODUCTION

The Division of Rare Diseases and Medical Genetics (DRDMG) requested that the Division of Pharmacovigilance-I (DPV-I) review the enhanced Pharmacovigilance (ePV) plan for fosdenopterin (NDA 214018) and photosensitivity. Fosdenopterin is a treatment for patients with molybdenum cofactor deficiency (MoCD) Type A, a rare, progressive, chronic, autosomal recessive inborn error of metabolism that typically exhibits an acute onset in neonates or in early infancy, usually with a fatal outcome. The request for ePV was prompted by potential photosensitivity detected in both in vitro and in vivo nonclinical studies. Female rats that received intravenous (bolus) administration of fosdenopterin at doses of 25, 50, and 100 mg/kg/day for three consecutive days followed by ultraviolet radiation exposure resulted in dose-dependent cutaneous skin reactions, and ophthalmic and histopathologic changes indicative of photosensitivity.¹

On October 23, 2020 an Information Request was sent to the sponsor communicating the activities for an ePV postmarketing plan including a follow-up targeted patient questionnaire.² The sponsor's proposed ePV plan and follow-up targeted patient questionnaire, was submitted to the FDA on November 9, 2020. The purpose of this review is to provide DPV-I's evaluation of the sponsor's proposed ePV plan and targeted questionnaire to better characterize the risk of photosensitivity with the use of fosdenopterin.

2 MATERIALS REVIEWED

DPV-I reviewed the sponsor's document dated November 9, 2020 entitled Fosdenopterin Pharmacovigilance Plan. The sponsor's pharmacovigilance plan includes details outlining the parameters to be followed and a Photosensitivity Adverse Event Questionnaire for follow-up for all reports of photosensitivity reported or identified. The draft ePV plan and targeted questionnaire is appended to this review in Appendix 5 and also available in Lorenz docuBridge.

The ePV plan@ <\\CDSESUB1\evsprod\nda214018\0033\m1\us\116-risk-management-plan\pv-plan-photosensitivity.pdf> and the

Photosensitivity Adverse Event Questionnaire @ <\\CDSESUB1\evsprod\nda214018\0033\m1\us\116-risk-management-plan\ae-photosensitivity-questionnaire.pdf>.

3 SUMMARY OF SPONSOR'S PROPOSED ENHANCED PHARMACOVIGILANCE PLAN

The sponsor proposes the following in addition to their routine pharmacovigilance practices, to further characterize the potential risk of photosensitivity with the use of fosdenopterin.

¹ Origin Biosciences, Inc. Response to the October 23, 2020 FDA Advice Letter. NDA 214018. FDA Received Communication Date: November 9, 2020.

² NDA 214018, Fosdenopterin. Information Request. Kong, Nicolas. October 23, 2020. DARRTS Reference ID: 4690779.

- Expedited Reporting: For a period of three years from approval, all initial and follow-up postmarketing Individual Case Safety Reports (ICSRs) identified by the Medical Dictionary for Regulatory Activities (MedDRA) Preferred Term (PT) “Photosensitivity reaction”, irrespective of the report’s origin and the event’s seriousness and expectedness, will be submitted as expedited 15-Day reports.
- Targeted Photosensitivity Adverse Event (AE) Follow-up Questionnaire: For all post-marketing ICSRs with a MedDRA PT of “Photosensitivity reaction”, a targeted follow-up questionnaire will be sent to the reporter to collect additional specific information on the photosensitivity reaction. In a case where the adverse event was reported by a patient or caregiver, the sponsor will request the patient or caregiver’s consent to contact their physician for filling in the targeted questionnaire. In case of ICSRs identified from literature, attempts will be made to collect the information from the author. The Targeted Questionnaire is appended to this review in Appendix 5.
- Interval and Cumulative Analyses in Periodic Safety Report: An interval and a cumulative summary analyses and a line listing summarizing each case with a photosensitivity reaction will be included in periodic safety reports. The analyses will include the sponsor’s causality assessment of all photosensitivity reports.

4 RECOMMENDATIONS

4.1 ENHANCED PHARMACOVIGILANCE PLAN

DPV-I recommends the following to be added to the sponsor’s proposed ePV plan:

- Expand the PTs in the MedDRA search strategy to include additional terms that may be coded and used when reporting and describing UVA skin and ophthalmic damage. These PTs should be used when searching and retrieving ICSRs from the safety database. Once the ICSR is retrieved and determined to be a report of photosensitivity it should prompt follow-up using the targeted questionnaires:
 - Actinic elastosis
 - Actinic prurigo
 - Administration site photosensitivity reaction
 - Burns first degree
 - Burns fourth degree
 - Burns second degree
 - Burns third degree
 - Injection site photosensitivity reaction
 - Infusion site photosensitivity reaction
 - Juvenile spring eruption
 - Photodermatosis
 - Photophobia
 - Photosensitivity reaction
 - Polymorphic light eruption
 - Solar dermatitis
 - Sunburn
- Due to the rarity of the indication for use, we will re-evaluate the ePV plan at three years post approval to determine if the ePV plan should be extended.

4.2 PHOTOSENSITIVITY TARGETED QUESTIONNAIRE

DPV-I recommends the following changes to the identified (caps and underlined) sections of the targeted questionnaire:

- OPENING PARAGRAPH: After “Please ensure personal patient information (such as full name and contact details of the patient) is not provided unless prior patient consent has been granted/obtained.” Add the following text “All the information and personal data you share with us will be protected and kept confidential in line with the Health Insurance Portability and Accountability Act (HIPAA) and applicable regulations.”
- PATIENT INFORMATION:
 - Gender. Change “gender” to “sex”. Sex is the demographic variable used by FDA.
 - Patient age group. Recommend identifying age groups as defined in “Guidance for Industry E11 Clinical Investigation of Medicinal Products in the Pediatric Population”:
 - Preterm (gestational age ___ weeks ___ days)
 - Neonate: Term (≥ 37 weeks gestation) and < 28 days old
 - Infant: 28 days to < 24 months
 - Children: 2 years to < 12 years
 - Patient height. Change to “height” to “height/length”.
 - Request patient ethnicity and race if not provided in Section E of initial MedWatch form.
- PATIENT MEDICAL HISTORY - To encourage greater detail concerning the event of interest separate question on any previous episodes of photosensitivity.
 - Has patient experienced previous episodes of photosensitivity to any other drugs?
Yes No
 - If yes, specify, erythema, tenderness, swelling, blistering, other?
 - Prior to fosdenopterin initiation were there any prior similar sun exposures without photosensitivity reactions? Yes No
- SUN EXPOSURE DETAILS
 - Add a section and ask about usual or typical sun exposure (e.g., total hours daily spent outdoors doing activities)
 - Include additional wording (underlined)
 - “In case of skin damage, have you planned or received a specific dermatologic consultation?”
 - “In case of ophthalmic damage, have you planned for or received a specific ophthalmology consultation?”

- ADVERSE EVENTS SUGGESTIVE OF PHOTSENSITIVITY
 - Description of clinical appearance to include a prompt for the percentage of Body Surface Area affected
 - Provide a photograph of the reaction if available
 - Change “Rational” to “Rationale” (typographical error)
 - Question to sponsor: Is the severity scale used in the questionnaire (i.e., mild, moderate, severe) standardized and validated? Reporter, if healthcare professional, base clinical assessment of severity grading on photographic scale.³

³ Larnier C et al (1994) Evaluation of cutaneous photodamage using a photographic scale. Br J Dermatol 130(2):167–173.

5 APPENDIX: PROPOSED ENHANCED PHARMACOVIGILANCE PLAN AND DRAFT TARGETED QUESTIONNAIRE SUBMITTED BY SPONSOR

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MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: December 17, 2020
Requesting Office or Division: Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number: NDA 214018
Product Name and Strength: Nulibry (fosdenopterin) for injection, 9,5 mg/vial
Applicant/Sponsor Name: Origin Biosciences, Inc. (Origin)
OSE RCM #: 2020-400-1
DMEPA Safety Evaluator: Sherly Abraham, R. Ph.
DMEPA Team Leader: Idalia E. Rychlik, Pharm.D.

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container labels and carton labeling received on December 11, 2020 for Nulibry. Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the revised container labels and carton labeling for Nulibry (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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^a Smith J. Label and Labeling Review for Nulibry (NDA 214018). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 NOV 25. RCM No.: 2020-400

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LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	November 25, 2020
Requesting Office or Division:	Division of Rare Diseases and Medical Genetics (DRDMG)
Application Type and Number:	NDA 214018
Product Name and Strength:	Nulibry (fosdenopterin) for injection, 9.5 mg/vial
Product Type:	Single ingredient Product
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Origin Biosciences, Inc. (Origin)
FDA Received Date:	October 23, 2020
OSE RCM #:	2020-400
DMEPA Safety Evaluator:	Sherly Abraham, R. Ph.
DMEPA Team Leader:	Idalia E. Rychlik, Pharm.D.

1 REASON FOR REVIEW

Origin Biosciences, Inc submitted NDA 214018 Nulibry (fosdenopterin)) for injection, on June 29, 2020 as part 3 of 3 of a rolling submission. Nulibry (fosdenopterin) was granted Breakthrough Therapy status for treatment of Molybdenum cofactor deficiency (MoCD) Type A. The Division of Rare Diseases and Medical Genetics (DRDMG) requested that we review the proposed Nulibry prescribing information (PI), instructions for use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B-N/A
Information Requests	C
FDA Adverse Event Reporting System (FAERS)*	D-N/A
Pro-Active Assessment	E
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 FINDINGS AND RECOMMENDATIONS

On June 29, 2020, Origin submitted their final proposed quality section and draft labels and labeling as part 3 of 3 of the rolling submission for NDA 214018. Nulibry (fosdenopterin) is a cyclic pyranopterin monophosphate (cPMP) substrate replacement therapy indicated for the treatment of patients with molybdenum cofactor deficiency (MoCD) Type A.

On August 6, 2020, we issued an information request (IR) to Origin regarding medication error safety concerns regarding their proposal for patient caregivers to reconstitute the proposed lyophilized powder in one or more vials with Sterile Water for Injection, USP, withdraw the accurate prescribed total dose volume and administer the product by an intravenous infusion using an infusion pump. We were concerned about the risk of preparation and administration errors by patient caregivers, leading to the administration of a wrong dose, given the complexity of the instructions. Therefore, we requested that Origin conduct a pro-active risk assessment to evaluate the potential risks associated with patient caregiver administration of their product.

On August 14, 2020, Origin submitted a pro-active risk assessment and concluded that the results of their assessment and their planned mitigation measures support the overall conclusion that use of Nulibry by patient caregivers in home setting is appropriate.

We reviewed the submitted pro-active assessment including PI, IFU, carton labeling and container labels. Due to the lack of human factors data to demonstrate that the proposed Instructions for Use (IFU) supports safe and effective use, we do not agree with Origin’s proposed use of the IFU as an acceptable risk mitigation strategy. However, following discussions with the clinical team, we note the public health benefit of this product for MoCD Type A as there are no approved treatment options for this ultra-rare, metabolic condition. We also note the favorable safety profile of Nulibry, with no death or drug related serious adverse events during the clinical evaluations. Furthermore, initiation of patient’s treatment is anticipated to occur in the in-patient hospital setting and patients are discharged with the coordination of physicians, home infusion pharmacies, and/or visiting home nurses. Per e-mail correspondence from DRDMG’s clinical reviewer, the safety profile of Nulibry at this point in the review is reassuring. The greatest clinical safety concern is the possibility of chronic underdosing resulting in a lack of efficacy which could lead to devastating neurologic consequences of the disease.

Taking into consideration the public health benefit associated with Nulibry and favorable safety profile, we find the administration of this product by patient caregivers, once deemed acceptable by a supervising physician and monitored thru home infusion and health services to be acceptable in this specific case.

Below, we provide recommendations to optimize the PI, IFU, carton labeling and container labels to help mitigate the risk of medication errors associated with the preparation and administration of Nulibry.

Tables 2 and 3 below include the identified medication error issues with the submitted prescribing information (PI), instructions for use (IFU), container labels, and carton labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

Table 2. Identified Issues and Recommendations for Division of Rare Diseases and Medical Genetics (DRDMG)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
1.	Use of confusing symbols or abbreviations(e.g., “>”, “<”, “GA” etc.)	The usage of symbols and abbreviations can cause	Replace the symbols and abbreviations with their intended meaning.

		misinterpretation and confusion. ^a	
2.	The use of trailing zeros are identified in the Dosing and Administration section in Highlights and Full Prescribing Information.	The use of trailing zeros may cause a ten-fold interpretation.	Remove the trailing zeros to avoid confusion.
Full Prescribing Information – Section 2 Dosage and Administration			
1.	As currently presented, important administration information regarding the involvement of physicians, home infusion pharmacy services and/or home health agencies for continuation of care outside the in-patient setting is missing from the PI.	Origin’s proactive assessment dated August 14, 2020, states that as patients transition from the hospital setting to the outpatient setting, the training for product preparation and administration is coordinated between patients, treating physicians, home infusion pharmacy services and/or a home health agencies. Yet, this administration statement is missing from the PI. As mentioned above in Findings and Recommendations, Origin has no human factors validation data to support their conclusion that their IFU is adequate to mitigate risks associated with caregiver administration of this intravenous infusion product at home. Therefore, we recommend that this statement is important to	We recommend adding the following the sentence in the beginning of section 2: <i>Coordination between patients, treating physicians, home infusion pharmacy services and/or home health agencies should be provided for administration of Nulibry in the outpatient setting.</i>

^a ISMP’s List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2015 [cited 2015 Sep 16]. Available from: <http://www.ismp.org/tools/errorproneabbreviations.pdf>.

		be added to the PI to ensure adequate training is provided by the transition team including home infusion services.	
2.	The important administration instruction statement stating the use of Nulibry is intended for use under the guidance of a healthcare provider and related sentences are lacking prominence.	Home use of Nulibry by patient caregivers is one of the most important information to be communicated to health care providers. This information should be prominently displayed to avoid confusion.	Relocate the important administration information paragraph to the primary position under Section 2, (b) (4) “
3.	As currently displayed, preparation instructions in step 1 do not include steps and a formula for calculating the total number of vials necessary per dose.	It is important to inform the healthcare provider how to calculate the dose so they may inform patient caregivers on how many vials are needed for total dose preparation.	Revise preparation instructions to add the directions for calculating the number of vials needed and total dose in mL needed.
4.	The storage information of the reconstituted drug is stated before the preparations steps in Section 2.2	Preparation and administration steps for this product is extremely important. Presenting important dosage and administration information to the reader in a text heavy format with decreased readability may lead to misinterpretation and medication preparation and administration errors.	Relocate the storage information of reconstituted drug to end of the section 2.2 under a subheading “Storage”.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The National Drug Code (NDC) number of the	Per 21 CFR 207.33 and 21 CFR 201.2, drug products	Add the NDC number of the container label in section 16.

	container label is missing.	subject to listing with the FDA is requested to have a unique NDC number to identify its labeler, product, and package size and type.	
Instructions for Use (IFU):			
1.	(b) (4)		
2.	Important administration information regarding the infusion rate lacks prominence and (b) (4) may cause confusion.	Embedding important preparation and administration information within text heavy formatting may lead to reader omission. Utilization of (b) (4) may confuse the user and cause delays in medication administration and/or medication use errors.	Bold the infusion rate statement and delete the (b) (4).
3.	The storage information is duplicated in two parts of the IFU, in the beginning under “Important Information You Need to Know Before Preparing and Injecting NULIBRY” and under “(b) (4)”.	Patient or caregiver may skim over the repetitive content and inadvertently miss important storage information.	Combine both sections of storage information and state them in the beginning under “Important Information You Need to Know Before Preparing and Injecting NULIBRY”.
4.	Preparation instructions for prescribed doses that require more than one vial lack prominence.	Some pediatric doses may require more than one vial. A lack of prominence of this information may lead to dosing errors.	In Step 6 (b) (4) (Dissolve) NULIBRY], we recommend bolding the sentence, “ Repeat steps 4 (b) (4) if more than one vial of NULIBRY is needed to (b) (4) ”

			(b) (4)

Table 3. Identified Issues and Recommendations for Origin Biosciences, Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling and Sample Container Label and Caron Labeling			
1.	The “Rx only statement” is overly prominent.	The increased prominence of the “Rx only statement” takes the reader’s attention away from other important information on the PDP such as established name, dosage form, and strength.	Decrease the prominence of the “Rx only statement” by decreasing the font size and unbolded.
2.	The format of the expiration date is undefined/incorrect.	The expiration date should be clearly defined to minimize confusion and risk for deteriorated drug medication errors.	Add the expiration date in the correct format. FDA recommends that the human- readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY- MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters

Table 3. Identified Issues and Recommendations for Origin Biosciences, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
3.	As currently displayed, the sample statement, "Sample-Not for Sale" has more prominence than other important information such as the proprietary name, established name, strength and dosage form.	PDP is reserved for the most important information such as the proprietary and established names, dosage form, and strength.	Relocate the sample statement, "Sample-Not for Sale" to the side panel or decrease the prominence of this statement.
Container Label and Sample Container Label			
1.	The strength statement lacks prominence.	Prominence and readability of the strength presentation is required per 21 CFR 201.15(a)(6).	Increase the prominence of the strength presentation. Consider relocating the strength statement to below dosage form similar to the carton labeling.
2.	As currently displayed on Principal Display Panel (PDP), the equivalency statement has more prominence than the product strength and dosage form and is located in close proximity to the strength statement.	PDP is reserved for the most important information such as the proprietary and established names, dosage form, and strength.	Decrease the prominence of the equivalency statement and to prevent confusion relocate it to the side panel.
3.	The net quantity statement is missing from the PDP.	21 CFR 201.51	Add a net quantity statement to the PDP.
4.	Usual Dosage statement, "Recommended Dosage: See prescribing information." is on the PDP.	PDP is reserved for the most important information. Other less important statements should be on the side panel.	Relocate the usual dosage statement to the side panel.
Carton Labeling and Sample Carton Labeling			

Table 3. Identified Issues and Recommendations for Origin Biosciences, Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
1.	The reconstitution statement, “Reconstitute prior to use” is on the side panel.	We recommend to state the reconstitution information on the PDP to minimize the risk of administration of the concentrated product.	Relocate the reconstitution statement from the side panel to PDP.
2.	The storage statement lacks prominence.	We recommend this to increase the prominence of this important information and minimize the risk of the storage information being overlooked.	Revise and bold the statement “ MUST BE FROZEN ”. Consider revising the storage statement on container label to “ MUST BE FROZEN ”.
3.	Post-reconstitution storage is missing from carton labeling.	These instructions will inform persons responsible for preparing the product and minimize the risk of administering expired products.	If space permits, information on post-reconstitution storage should also be included on the carton labeling.

4 CONCLUSION

Our evaluation of the proposed Nulibry prescribing information (PI), instructions for use (IFU), container labels, and carton labeling identified areas of vulnerability that may lead to medication errors. Above, we have provided recommendations in Table 2 for the Division and Table 3 for the Applicant. We ask that the Division convey Table 3 in its entirety to Origin Biosciences, Inc. so that recommendations are implemented prior to approval of this NDA.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Nulibry that Origin Biosciences, Inc. submitted on October 23, 2020.

Table 4. Relevant Product Information for Nulibry													
Initial Approval Date	N/A												
Active Ingredient	fosdenopterin												
Indication	The treatment of patients with molybdenum cofactor deficiency (MoCD) Type A												
Route of Administration	intravenous infusion												
Dosage Form	for injection												
Strength	9.5 mg/vial												
Dose and Frequency	<u>Pediatric patients less than 12 months</u> – Dosage should be titrated to the target dose of 0.9 mg/kg/day over a period of 3 months. <table border="1"> <thead> <tr> <th>Titration Schedule</th> <th>Gestational Age ≥ 37 weeks mg/kg</th> <th>Gestational Age < 37 weeks mg/kg</th> </tr> </thead> <tbody> <tr> <td>Initial Dose</td> <td>0.55 mg</td> <td>0.40 mg</td> </tr> <tr> <td>Month 1</td> <td>0.75 mg</td> <td>0.70 mg</td> </tr> <tr> <td>Month 3</td> <td>0.90 mg</td> <td>0.90 mg</td> </tr> </tbody> </table> <u>Patients 1 year or older</u> - the recommended dosage is 0.90 mg/kg administered once daily.	Titration Schedule	Gestational Age ≥ 37 weeks mg/kg	Gestational Age < 37 weeks mg/kg	Initial Dose	0.55 mg	0.40 mg	Month 1	0.75 mg	0.70 mg	Month 3	0.90 mg	0.90 mg
Titration Schedule	Gestational Age ≥ 37 weeks mg/kg	Gestational Age < 37 weeks mg/kg											
Initial Dose	0.55 mg	0.40 mg											
Month 1	0.75 mg	0.70 mg											
Month 3	0.90 mg	0.90 mg											
How Supplied	Nulibry (fosdenopterin) for injection is supplied as a sterile, lyophilized powder in a single-dose clear glass vial for intravenous infusion after reconstitution. Each Nulibry vial contains 9.5 mg of fosdenopterin. Each carton of Nulibry contains one vial of lyophilized powder for reconstitution (NDC 73129-001-01).												
Storage	Store un-reconstituted Nulibry frozen between –25°C and –10°C (–13°F and 14° F). Store the vial in its original carton to protect from light.												

APPENDIX C. INFORMATION REQUEST:

Information request dated August 6, 2020 and response from Origin received on August 14, 2020:

We understand that you are planning to use Nulibry for injection to treat patients with molybdenum cofactor deficiency (MoCD) Type A. We note you propose Nulibry as a lyophilized powder, in a single-dose vial, which is intended to be prepared and administered by a patient's caregiver at home, as long as a healthcare provider determines that is appropriate. The preparation and administration steps for Nulibry are complex; they require the caregiver to calculate the appropriate number of vials needed in order to achieve the prescribed dose, reconstitute each vial of lyophilized powder with diluent, withdraw an accurate prescribed total dose volume and administer the infusion. We are concerned about the risk of preparation and administration errors that could inadvertently result in the administration of a wrong dose.

We recommend you conduct a proactive risk assessment if you have not already completed one. The proactive risk assessment should include a comprehensive and systematic evaluation of all the steps involved in using your product, the errors that users might commit or the tasks they might fail to perform, and the potential negative clinical consequences of use errors and task failures. Your risk assessment should also discuss risk-mitigation strategies you intend to employ to reduce risks you have identified to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

The following final and draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for product design and labeling³:

- Guidance on Safety Considerations for Product Design to Minimize Medication Errors*
- Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*
- Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications*

Please submit your proactive risk assessment to the Agency for review and comment. You may submit the requested information under NDA 214018 in eCTD Section 5.3.5.4 – Other Study reports and related information.

1.2 Regulatory Background

Based on the favorable safety profile of Nulibry, with no deaths or drug related SAEs and no serious safety concerns determined during the clinical evaluations, the safety profile is positive for this patient population. Considering this safety profile, as well as the Agency's feedback ([Pre-NDA Clinical Meeting of 18 December 2019](#)) that a REMS will likely not be needed for fosdenopterin, Origin provided draft labeling in the NDA that includes [Full Prescribing Information](#) to inform physicians and [Instructions for Use \(IFU\)](#) which outlines the proper use of the drug for patient's caregivers. Origin also provided draft labeling for the NULIBRY [carton](#) and [vial](#).

Origin developed the proposed draft labeling in accordance with the regulations and applicable FDA Guidances, including the Guidance for Industry *Instructions for Use — Patient Labeling for Human Prescription Drug and Biological Products and Drug-Device and Biologic-Device Combination Products — Content and Format*. The administration of NULIBRY is a multifaceted process and the IFU was developed to capture and communicate the critical steps of use in a clear manner for the layperson to understand and follow.

Origin is interested in receiving the Agency's feedback and collaborating on the proposed IFU during the course of the NDA review.

2 RESPONSE TO REQUESTED INFORMATION

As requested, Origin has conducted a Proactive Risk Assessment to provide comprehensive and systematic evaluation of all the steps involved in using NULIBRY. The [Proactive Risk Assessment](#) is provided in Module 5.3.5.4, as recommended by FDA.

In summary, the results of this use related risk analysis together with the planned mitigation measures support the overall conclusion that use of NULIBRY in the home setting is appropriate. The proposed draft labeling, IFU, and container and carton labels are sufficient to ensure an acceptable level of risk of medication errors that would result in a significant safety issue, particularly in light of the overall safety profile of the drug. See the [Proactive Risk Assessment](#) document for recommendations proposed by Origin for the IFU.

APPENDIX E. PRO-ACTIVE ASSESSMENT

Origin submitted their pro-active risk assessment on August 14, 2020:



proactive-risk-assessment.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^b along with postmarket medication error data, we reviewed the following Nulibry labels and labeling submitted by Origin Biosciences, Inc.

- Container label(s) received on October 23, 2020
- Carton labeling received on October 23, 2020
- Instructions for Use and Prescribing Information (Image not shown) received on October 23, 2020
<\\CDSESUB1\evsprod\nda214018\0030\m1\us\114-labeling\draft\labeling\pi-and-ifu-revised-clean.docx>

F.2 Label and Labeling Images

(b) (4)



3 Page(s) of Draft Labeling have been Withheld in Full as B4 (CCI/TS) immediately following this page

^b Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

SHERLY ABRAHAM
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MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 11/12/2020

TO: Division of Rare Diseases and Medical Genetics (DRDMG)
Office of Rare Diseases, Pediatrics, Urology and Reproductive Medicine (ORPURM)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 214018

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not warranted at this time for the site listed below. The rationale for this decision is noted below.

Rationale

OSIS conducted a Remote Regulatory Review (RRR) for the site in July 2020, which falls within the surveillance interval. The RRR was conducted under the following submissions: [REDACTED] (b) (4)

OSIS concluded that data from the reviewed studies were reliable.

Therefore, based on the rationale described above, an inspection is not warranted at this time.

RRR Site

Facility Type	Facility Name	Facility Address
Analytical	[REDACTED]	[REDACTED] (b) (4)

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